Long-term follow-up of acute changes in corona artery diameter caused by Kawasaki disease: risk factors for development of stenotic lesions

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Abstract: OBJECTIVE: To investigate the long-term outcome of initially dilated/aneurysmatic coronary arteries in Kawasaki disease (KD) and to define risk factors for significant myocardial ischemia during follow-up, we retrospectively followed all pediatric patients with proven acute coronary changes due to KD in our institution. METHODS AND RESULTS: Since 1981, 38 children have been identified with coronary changes due to KD. The median age was 1.2 years (0.1-12.8). In 37 patients therapy with intravenous immunoglobulin was initiated within 9 days (1-30) after the beginning of KD. All received aspirin and three additionally received steroids. Median follow-up was 8.5 years (0.5-24.8). We defined two groups: A aneurysm/ectasia of the coronary artery < or =5.0 mm (n = 23) and B aneurysm size >5.0 mm (n = 15). During follow-up, all coronary aneurysms of group A regressed to normal size, whereas in 14 patients of group B (93%) the aneurysms persisted or even increased in size. Four patients of group B developed severe coronary stenosis at the proximal and/or distal end of the aneurysm and needed an intervention (endovascular balloon dilation and stent implantation (n = 2) or bypass surgery (n = 2)) after a median time interval of 9.8 years (1.0-15.6) after KD. They all had ECG changes preceding the intervention about 1 year in advance. Maximum aneurysm size >5 mm was a statistical significant predictive risk factor for myocardial ischemia. CONCLUSIONS: After KD, patients with a coronary aneurysm size >5.0 mm need close follow-up assessments because of an elevated risk for the development of coronary stenotic lesions. In case of new and even unspecific ECG changes, coronary imaging modalities (angiography, MRI) have to be considered. Therapy options vary from percutaneous catheter interventions to bypass surgery and have to be selected individually for each patient.

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ORIGINAL PAPER

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Objective To investigate the long-term outcome of initially dilated/aneurysmatic coronary arteries in Kawasaki disease (KD) and to define risk factors for significant myocardial ischemia during follow-up, we retrospectively followed all pediatric patients with proven acute coronary changes due to KD in our institution.
Methods and results Since 1981, 38 children have been identified with coronary changes due to KD. The median age was 1.2 years (0.1–12.8). In 37 patients therapy with intravenous immunoglobulin was initiated within 9 days (1–30) after the beginning of KD. All received aspirin and three additionally received steroids. Median follow-up was 8.5 years (0.5–24.8). We defined two groups: A aneurysm/ectasia of the coronary artery $\leq$5.0 mm ($n = 23$) and B aneurysm size >5.0 mm ($n = 15$). During follow-up, all coronary aneurysms of group A regressed to normal size, whereas in 14 patients of group B (93%) the aneurysms persisted or even increased in size. Four patients of group B developed severe coronary stenosis at the proximal and/or distal end of the aneurysm and needed an intervention (endovascular balloon dilation and stent implantation ($n = 2$) or bypass surgery ($n = 2$)) after a median time interval of 9.8 years (1.0–15.6) after KD. They all had ECG changes preceding the intervention about 1 year in advance. Maximum aneurysm size >5 mm was a statistical significant predictive risk factor for myocardial ischemia.
Conclusions After KD, patients with a coronary aneurysm size >5.0 mm need close follow-up assessments because of an elevated risk for the development of coronary stenotic lesions. In case of new and even unspecific ECG changes, coronary imaging modalities (angiography, MRI) have to be considered. Therapy options vary from percutaneous catheter interventions to bypass surgery and have to be selected individually for each patient.

Keywords Kawasaki disease · Coronary aneurysm · Stenotic lesions · Intervention · Long-term follow-up

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Introduction

Kawasaki disease (KD) is the most common cause of multisystem vasculitis in childhood. Since its first description by Tomisaku Kawasaki [13], it has now replaced rheumatic fever as the number one acquired heart disease in children of the developed world, due to its predilection for the coronary arteries [23, 25, 31].

The disease is still associated with the mortality, mostly due to the coronary artery changes. Giant aneurysms can occur, and are unlikely to resolve, and may develop stenosis during follow-up with the risk of coronary thrombosis, myocardial infarction and death [1, 2, 5, 6]. Therefore, the early detection of indicating factors can be of great benefit [8].

The objective of this study was to present the long-term follow-up of pediatric patients with coronary changes due to KD, and to define predictive risk factors for significant

myocardial ischemia after KD requiring an intervention during follow-up, and to describe different therapy options for these specific obstructive lesions.

Methods

Patients and study design

In this retrospective study, we followed all patients with acute coronary artery changes due to KD between December 1981 and 2005. The following variables were analyzed: age at onset of the disease, gender, localization and aneurysm size of affected coronary artery, and onset of acute therapy for KD. During follow-up, we investigated the course of aneurysm size, abnormalities of electrocardiography (ECG), therapy of coronary artery stenosis, and outcome of interventions for stenotic lesions.

Routine follow-up assessment includes physical examination, ECG, echocardiography and ergometric exercise testing. We do not routinely perform other tests to evaluate possible coronary stenosis and myocardial ischemia in every patient after KD. But in patients with known coronary involvement greater than or equal to risk level III (isolated small to medium coronary aneurysm in $\geq$1 coronary artery) we perform stress tests with myocardial perfusion [perfusion magnetic resonance imaging (MRI)] every 2 years (every year in patients with risk level IV and V) in pts >10 years, according to the recommendations of the American Academy of Pediatrics [21]. In addition, coronary angiographies or magnetic resonance imaging (MRI) perfusion scans were performed in patients with abnormalities in ECG, pathologic changes during exercise testing or clinical episodes of chest pain.

For further risk factor analysis, we defined two groups of the size of coronary arteries: *group A* with coronary aneurysm/ectasia $\leq$5.0 mm, *group B* with coronary aneurysm >5.0 mm.

Approval was obtained from the local ethics committee.

Statistical analysis

Data are given as median and range. Intervention-free course after diagnosis of KD was analyzed by the Kaplan–Meier method, and differences were assessed by the log-rank test. Predictive risk factors, such as age, sex, begin of IVIG therapy, size of coronary ectasia/aneurysm, localization of coronary aneurysm (RCA vs. LCA), and ECG abnormalities during follow-up for the development of coronary artery stenosis were analyzed with Cox regression.

A P value <0.05 is considered statistically significant. Statistical analysis was performed using SPSS 12 for MacOSX^{TM} (Chicago, IL).

Results

Patients and clinical course

Thirty-eight patients were diagnosed with acute coronary changes/dilatations due to KD, which reflects an incidence of coronary changes in 21% of all patients during this time period. The age at onset of KD in the 38 afflicted patients ranged from 0.1 to 12.8 years (median 1.2 years). The patients were mainly male (male:female = 24:14). Left coronary artery (LCA) was more often affected than right coronary artery (RCA) (Table 1). In 37 of 38 cases, intravenous immunoglobulin (IVIG) therapy was started after a median of 9 days (1–440 days) after the onset of KD. In addition, three patients received steroids. One patient did not receive IVIG or steroids due to the late diagnosis. High-dose aspirin (ASA) was initially given to all patients (Table 2).

During follow-up, all patients with known coronary aneurysms were left on low-dose ASA, at least until the aneurysm regressed. Patients with giant aneurysms received an oral anticoagulation with marcumar [20].

Follow-up time after KD was 8.5 (0.1–24.8) years—for patients in group A 6.4 (0.5–18.8) years and for patients in group B 8.7 (0.9–24.8) years.

Coronary arteries

According to their maximum size of coronary artery dilatation, 23 patients belonged to group A (coronary aneurysm/ectasia $\leq$5.0 mm), and 15 patients to group B (coronary aneurysm >5.0 mm).

During follow-up, all coronary aneurysms of group A regressed to normal size, whereas in 14 patients of group B (93%) the aneurysms persisted or even increased in size (Fig. 1).

Table 1 Characteristics of 38 patients, who have been detected with acute coronary artery changes during Kawasaki disease

Patient data (n = 38)	
Age at onset of KD (years)	1.2 (0.01–12.8)
Sex (M:F)	24:14
Therapy begin after onset of KD (days)	9 (1–440)
Affected coronary—LCA: RCA	31:7
Maximum aneurysm size	5 (2.8–23)
Group A (coronary aneurysm/ectasia $\leq$5.0 mm)	n = 23
Group B (coronary aneurysm >5.0 mm)	n = 15
Follow-up (years)	8.5 (0.5–24.8)

Values are expressed as median and range

LCA left coronary artery, *RCA* right coronary artery

Table 2 Characteristics of the study groups

Coronary aneurysm/ectasia size	Group A (≤5.0 mm)	Group B (>5.0 mm)
Number of patients	23	15
Age at onset of disease (years)	1.3 (0.02–12.8)	0.8 (0.2–10.1)
Sex (M:F)	16:7	8:7
Maximum aneurysm size (mm)	3.5 (2.8–5.0)	8.0 (5.8–23.0)
Interventions	0	4

Values are expressed as median and range

Four patients with a coronary aneurysm size >5 mm (27% of group B) developed severe coronary artery stenosis at the proximal or distal end of the aneurysm requiring an intervention after a median interval of 9.8 years (Table 4).

Therefore, the intervention-free course after diagnosis of KD is shown in Fig. 2.

A diameter of the coronary ectasia/aneurysm >5.0 mm during or after acute KD is a predictive value for the development of stenotic coronary lesions ($P = 0.04$).

Electrocardiography abnormalities during follow-up were registered in five patients. They were partly combined with clinical symptoms of myocardial ischemia, which occurred several months later. Diagnostic work up confirmed severe obstructive coronary lesion by perfusion MRI in two, selective coronary angiography in two and could be excluded in one patient. ECG abnormalities are a predictive risk factor ($P = 0.0001$).

Differences in age, gender, localization of coronary aneurysm and the onset of IVIG therapy did not have a significant influence (Table 3).

Interventions (Table 4)

Two of the four patients with significant coronary stenosis during follow-up primarily received an endovascular intervention for their coronary stenosis. They developed their stenosis late after initial KD, with an interval of 15.5 and 14.7 years, respectively. In both cases, unspecific ECG changes and in one case additional symptoms as exercise-induced dyspnea and syncope, which occurred 10 months after these initial ECG changes, led to further investigations. MRI perfusion scan demonstrated a perfusion defect at first pass in the territory of the left anterior descending artery (LAD) in both patients (Fig. 3). This single vessel disease was intended to be treated percutaneously in both. Coronary arterial angiography confirmed the singular severe and partly calcified stenosis at the proximal end of the former aneurysm site (Fig. 4). A percutaneous transluminal coronary angioplasty (PTCA) alone was not successful in these calcified stenotic vessels. Therefore, both patients received an additional coronary stent implantation, one coronary bare metal stent (BMS) and one drug-eluting stent (DES), with a satisfactory result. Despite an adequate antiplatelet therapy with ASA (100 mg per day) and clopidogrel (75 mg per day), one patient suffered from a complete thrombotic occlusion of the implanted stent 1 month after intervention. Taking into account the age of the young patient, and the morphology, and vulnerability of the affected coronary, he then received a coronary bypass operation utilizing the pedicled internal thoracic artery. The peripheral coronary perfusion was restored, no cardiac sequelae occurred.

Two other patients with large (giant) and bilateral coronary aneurysms without any significant regression primarily received a surgical revascularization for their coronary stenosis. Both patients complained of subjective symptoms of myocardial ischemia during exercise, 1 and 4.7 years after KD, respectively. Unspecific ECG changes had already been registered about 1 year in advance in both patients. A selective coronary arteriography revealed a complete occlusion of the RCA and LAD with insufficient collateral circulation in one patient, and in the other one a severe stenosis (>90%) of the RCA and LAD. The stenotic lesions were localized at the proximal and/or distal end of the aneurysms. A combined surgical approach with the resection of the large aneurysms (aneurysmectomy) and bypass surgery was chosen in both cases. One patient received a bilateral anastomosis of his internal thoracic artery with LAD and RCA, and two supplementary venous

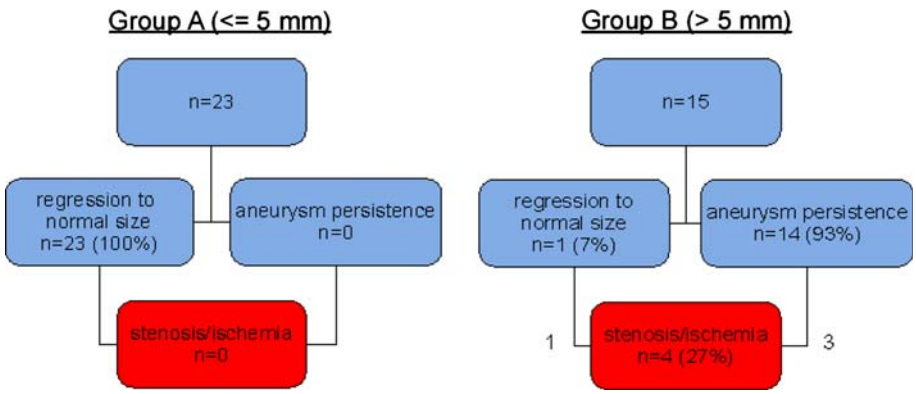

Fig. 1 Fate of initial coronary aneurysms during follow-up

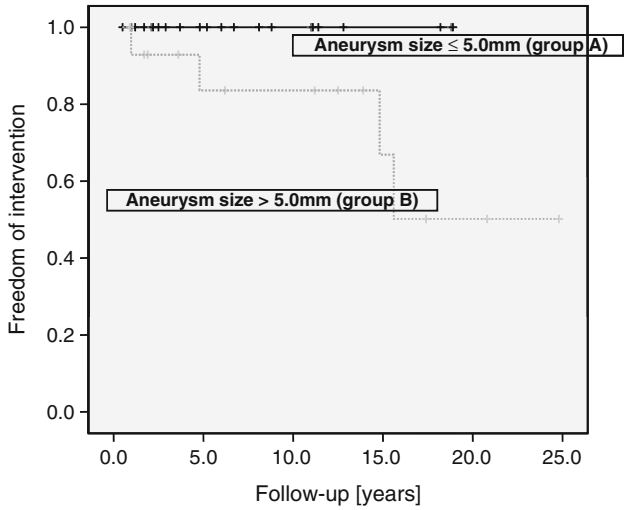

Fig. 2 Kaplan–Meier survival analysis demonstrating the intervention-free course after diagnosis of KD in patients with coronary aneurysm/ectasia size ≤5.0 mm (*group A*) and with aneurysm size >5.0 mm (*group B*). The course of both groups was significantly different ($P < 0.04$)

Table 3 Influence of different continuous variables on event-free survival after KD analyzed with Cox regression

Risk factor	*P* value
Age	0.299
Sex	0.114
LCA versus RCA	0.582
Therapy (IVIG) delay	0.950
ECG changes	0.0001
Aneurysm size	0.008
Group A versus group B	0.004

A *P* value <0.05 was considered statistically significant

grafts of autologous saphenous veins (CABG coronary artery bypass grafting). Although a standard antiplatelet therapy with ASA was initiated, a control angiography 6 months after surgery showed a complete occlusion of both venous grafts and patent arterial grafts. Without any signs of considerable myocardial ischemia, further percutaneous or surgical interventions were not necessary. In the other patient, a single arterial bypass of his left internal thoracic artery to LAD was sufficient to restore complete coronary perfusion, beside the bilateral aneurysmectomy. Control angiography after 6 months showed a patent arterial bypass. 8 years after the operation, the patient is still doing well without any clinical signs of myocardial ischemia.

Discussion

Morbidity and mortality of KD still exist mostly because of its predilection for the coronary arteries. Acute coronary changes/dilatations can occur in 10–20% of KD patients [8, 21, 23]. They comprise coronary vasculitis with the destruction of the internal elastic lamina, thrombocytosis and hypercoagubility. Accordingly, in our patient group, the rate of acute coronary affection/dilatation was 21%.

Many previous studies have looked at putative predictors of acute coronary artery lesion development in KD. They investigated demographic, clinical, and laboratory variables [3, 9, 15]. Male gender, young age at diagnosis, long duration of fever, and low-serum albumin level have been identified as high-risk factors. Harada [9] suggested a set of high-risk criteria to facilitate a rationale decision-making for IVIG therapy.

After the acute phase, histopathological findings show an arterial remodeling with more or less progressive thickening of the intima because of smooth muscle cell proliferation, followed by a neoangiogenese of microvessels and a fibrotic proliferation [21]. Approximately 50% of coronary aneurysms occurring in the acute stage of the disease were shown to regress within several years [10, 12]. Smaller, as well as fusiform, rather than saccular, and distally located aneurysms have a greater likelihood of regression [19].

However, the risk of thrombotic occlusion and sudden cardiac death remains for some patients [30].

The primary question addressed in this study is possible risk factors for the development of significant coronary artery lesions during long-term follow-up.

In our patient group of 38 patients with detectable coronary aneurysms/ectasias due to KD, we were able to show that during follow-up 93% of all aneurysms sized >5 mm persisted or even increased in size, whereas smaller aneurysms all regressed completely. 15.5 years after KD, already 25% of the patients with an initial aneurysm size >5 mm had developed severe coronary stenosis at the proximal and/or distal end of the aneurysm and needed an intervention, either surgically or by catheter intervention. Maximum aneurysm size >5 mm was a statistical significant predictive risk factor for late myocardial ischemia. Age, gender, localization of coronary aneurysm, and the beginning of IVIG therapy did not have a significant influence.

Giant aneurysms with a maximum diameter ≥8 mm have been reported to have the worst prognosis with regard to the development of significant coronary stenosis [26, 27]. Progressive myointimal proliferation in combination with sluggish blood flow within the extremely dilated vessels and continuous thrombus apposition can cause the fatal vessel narrowing, typically at the proximal or distal end of the aneurysm [10, 15]. Beside these structural abnormalities, coronary ischemia may also result in late functional abnormalities of the coronary endothelium with abnormal vasoreactivity [7]. After several years, at least

Table 4 Specific data of four patients with coronary arterial stenosis requiring a coronary intervention during follow-up (Primarily percutaneous intervention in cases 1 and 2, primarily bypass surgery in cases 3 and 4)

	1	2	3	4
Sex	F	M	F	F
Age at onset of KD (years)	0.26	0.46	0.24	9.67
Max. aneurysm size (mm)	8	7.5	23	10
Interval disease—procedure (years)	15.5	14.7	4.7	1
Age at procedure (years)	16	15.2	5	10.6
Intervention site	LAD	LAD	LAD/RCA	LAD/RCA
Symptoms	Syncope, dyspnea	–	Angina pectoris	Angina pectoris
ECG changes	Yes	Yes	Yes	Yes
MRI/Angiography	+/+	+/+	−/+	−/+
Procedure	PTCA and BMS	PTCA and DES	2 × CAB/2 × ACVB Aneurysm-ectomy	1 × CAB Aneurysm-ectomy
Complications of the procedure	No	No	No	No
Follow-up after procedure (years)	0.6	0.6	7.9	8
Patency of coronary/grafts	Restenosis after 1 month	Open	Occlusion of venous graft	Open
Re-intervention	CAB	–	–	–

LAD left anterior descending artery, *RCA* right coronary artery, PTCA percutaneous transluminal coronary angioplasty, BMS bare-metal coronary stent, *DES* drug-eluting coronary stent, *ACVB* aortocoronary venous bypass, *CAB* coronary arterial bypass

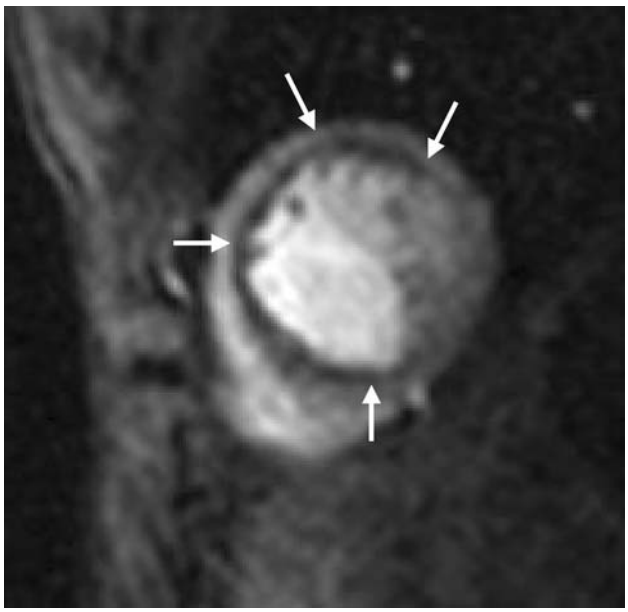

Fig. 3 Magnetic resonance imaging scan demonstrating first-pass perfusion defect of the LAD territory in a patient with total occlusion of LAD

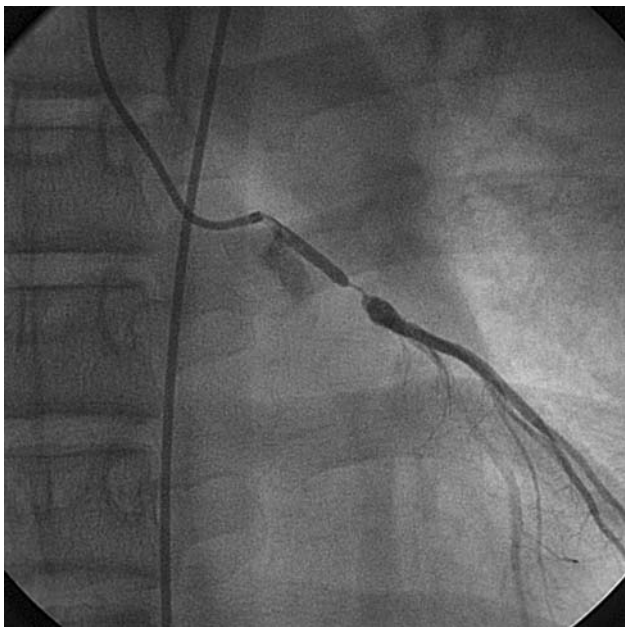

Fig. 4 Coronary arterial angiography showing the singular severe stenosis at the former aneurysm site in the proximal LAD. The stenosis is located at the proximal end of the residual aneurysm and is partly calcified

6–8 years, the coronary vascular stiffness may additionally be deteriorated by progressive calcifications [1, 11].

The time-span between the onset of the disease and development of coronary stenosis varies from several months to 45 years [26, 28, 29]. Also in our patients with significant coronary stenosis requiring an intervention this time interval varied from 1 to 15.5 (median 9.8) years.

All of them had ECG changes preceding the intervention about 1 year in advance. These unspecific ECG changes had a highly significant predictive value for coronary obstructions during follow-up after KD ($P = 0.0001$).

Different imaging modalities exist to confirm the suspected coronary lesion after KD. Echocardiography allows to measure proximal coronary artery dimensions. In addition, it also may reveal the lack of normal tapering and perivascular echogenicity. X-ray coronary angiography is the classic technique to evaluate coronary arteries more exactly, but it is an invasive and radiation method. MRI has proven to be a valuable tool to evaluate the coronary artery origin and proximal course in children and adults with KD [17, 18]. It also has the advantage of simultaneous perfusion, function, and viability evaluation [17]. However, there are limitations to reliably detect coronary artery lesions and perfusion defects in small children with higher heart rates. In small children, X-ray coronary angiography is still preferred to give a more accurate overview of coronary anatomy. In adolescents and adults, if MRI is not available, a combination of echocardiography and single-photon emission computed tomography (SPECT) can be an alternative to demonstrate anatomy, function, and perfusion of the coronary arteries [17].

Therapy options for significant early- and late-coronary artery stenosis in patients with KD vary from surgical bypass insertion to different catheter interventional procedures. In adults with coronary artery disease catheter interventions are well established and undoubtedly of high clinical value. However, in patients with KD, only limited experiences and results with catheter interventions have been reported [1, 2, 11, 20, 22, 24]. The success rate of PTCA in patients with KD and coronary artery stenosis seems to be limited due to a marked initimal thickening with a high recoil capacity within the first years after acute KD, and due to multiple calcifications with severely reduced compliance of the arterial wall after long-term KD [2, 11, 24]. High-pressure balloons with a maximum balloon pressure >10 atm, which have been used in this situation, may lead to late neoaneurysm formation [2, 11, 24]. Moreover, the incidence of restenosis after PTCA has been reported to be increased with a rate of 24% [2]. Nevertheless, PTCA has shown to be effective in selected cases [20], especially in patients without severe calcification or in patients with a relatively short interval between the onset of the disease and the intervention.

In both of our patients, who received an interventional treatment of their coronary stenosis, PTCA was not successful and stent implantation was necessary. Stent placement has been useful in older children with mild calcifications and in children with giant aneurysms [11]. It can be preferable to PTCA, because it may prevent new aneurysm formation and restenosis [2, 4, 11, 24]. In patients with severe calcified coronary stenosis percutaneous transluminal coronary rotational ablation (PTCRA) may be the only effective interventional treatment option [2, 11, 16, 24, 29]. High success rates >80% even in severe calcifications justify its use and make it the option of choice in this patient group [2, 16, 24, 29]. It is also recommended in cases where PTCA and/or stent implantation was not successful.

At present, coronary artery bypass grafting (CABG) is the preferred surgical treatment procedure for revascularization of ischemic myocardium due to stenotic lesions after KD, using either a saphenous vein—with less good results—or the internal thoracic artery. Compared with catheter interventions, bypass surgery is preferred in patients, who have vessels with multiple, ostial, or long-segment lesions, and/or in patients with severe left ventricular dysfunction [14, 21, 28, 32].

In our patients, all arterial grafts seem to be patent during mid-term follow-up, whereas all venous grafts (in one patient) showed complete occlusion within 1 year despite an adequate anticoagulation regime.

The long-term results of arterial bypass grafting in KD patients are encouraging. In a large published series with 100 patients, the patency rates were 94, 82, and 78% at 1, 5, and 10 years, respectively, whereas patency rates for venous grafts were only 82, 63, and 36%, respectively [32]. Arterial internal mammary grafts may grow according to the somatic growth of children, by this having the potential to serve as "live" conduit in pediatric patients [14, 32]. In young children, vessel diameters are small, which may result in postoperative stenosis at the anastomotic site. PTCA has been used successfully in pediatric patients after KD for treating anastomotic stenosis. In a recently published series, the long-term results of internal thoracic artery bypasses in children <12 years have improved significantly through PTCA for anastomotic stenosis and the application of appropriate indications. The patency rates in this patient group were >90% at 20 years [28].

Conclusions

Approximately 16% of the patients with initial coronary aneurysms developed stenotic lesions with myocardial ischemia requiring therapy during follow-up. The most significant risk factor for the development of stenotic lesions is an aneurysm-size >5.0 mm. ECG changes may precede symptomatic ischemia for months. In case of new and even unspecific ECG changes, advanced coronary imaging modalities (angiography, MRI) have to be considered.

Therapy options vary from percutaneous catheter interventions (PTCA, stent implantation, PTCRA) to bypass surgery and have to be selected individually for each patient. In our very limited experience, internal mammarial artery bypass surgery has shown excellent mid-term results in patients with coronary lesions after KD.

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